0.8 mg/kg often failed to achieve our target AUC of 1150–1350. Fifteen AML/MDS patients receiving 0.8 mg/kg had a mean AUC of 1059 (822–1653), with 12 AUCs < 1150. Subsequently, our routine starting dose of IV Bu was changed to 0.9 mg/kg.

Methods: We performed a retrospective review of AML and MDS patients from an IRB approved HIPAA compliant database established for the collection and analysis of Bu PK. Data from two groups of Bu patients treated between 1998 and 2008 were analyzed. Fifty-eight patients were treated with oral Bu (1 mg/kg) and fifty-eight patients were treated with IV Bu (0.9 mg/kg). Bu AUC was determined for the first dose and adjustments were made on subsequent doses to target an AUC of 1150–1350.

Results: Median age for IV and oral Bu patients was 42 (18–68) and 47 (23–67), respectively (p = 0.0049). The mean terminal half-life ($T_{½}$) was 186 minutes (131–253) for IV Bu and 181 minutes (110–305) for oral Bu (p = NS). Mean AUCs were 1115 (777–1569) for IV Bu patients and 1260 (654–2019) for oral Bu (p = 0.0094). Seventeen (29.3%) patients in each group achieved AUCs within our target of 1150–1350. Thirty-four (58.6%) IV Bu patients had AUCs < 1150 compared to twenty (34.5%) oral Bu patients (p = 0.0092). Eight (13.8%) IV Bu patients had AUCs >1350 compared to twenty-one (36.2%) oral Bu patients (p = 0.0053).

Conclusions: While first dose PK analysis showed similar $T_{½}$ for IV and oral Bu, the AUCs achieved with 0.9 mg/kg IV Bu are lower than with 1mg/kg oral Bu dosing. First-dose AUC from recipients of IV Bu had a lower variance than AUC from recipients of oral Bu. Despite changing our starting IV Bu dosing from 0.8 mg/kg to 0.9 mg/kg, the majority of patients still require therapeutic drug monitoring with dose adjustments to obtain our desired target AUC of 1150–1350.

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A RETROSPECTIVE ANALYSIS OF RISK FACTORS THAT INFLUENCE INTRAVENOUS BUSULFAN KINETICS IN ADULT PATIENTS

McBride, A.[1], Fancher, K.[1], Perkins, J.[1], Milone, M.[2], Shaw, L.[2], Conwell, M.[1] [1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [2]Hospital of the University of Pennsylvania, Philadelphia, PA

Busulfan (Bu) is a bifunctional alkylating agent that is a common component of conditioning regimens prior to hematopoetic stem cell transplantation (HSCT). Bu pharmacokinetics, either with area under the curve (AUC) or average concentration at steady state (C_{ss}), can be utilized to evaluate efficacy and prevent adverse effects such as hepatic veno-occlusive disease (VOD). Pharmacokinetic models that predict Bu levels were historically performed with q 6 hour oral dosing in the pediatric population and used a limited linear regression model. Since the advent of intravenous (IV) Bu, a consistent pharmacokinetic modeling system based on specific patient parameters has not emerged. Likewise, current Bu pharmacokinetics models may not be accurate in adult patients or with once-daily dosing schedules. We will report a retrospective study of approximately 300 patients and present a predictive pharmacokinetic model for appropriate AUC with once-daily IV Bu in adult patients. Our model will be based on first dose kinetic analyses. We will also evaluate currently published risk factors that may influence IV Bu kinetic parameters using univariate, multivariate and stepwise Cox regression analyses. Age, race, gender, disease state, disease status at time of transplantation, number of previous chemotherapy regimens, renal and hepatic function at time of transplant and graft source will be evaluated. Long-term outcomes to be examined include overall mortality, probability of survival, development of acute and chronic graft versus host disease (GVHD), development of VOD and days until neutrophil and platelet engraftment. Statistical model design and specific data results will be presented at the 2009 ASBMT Annual Conference.

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AN ANALYSIS OF TOXICITIES AND TIME TO ENGRAFTMENT ASSOCIATED WITH THREE DISTINCT MELPHALAN TREATMENT SCHEMAS IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING AUTOLOGOUS HEMATOPOETIC STEM CELL TRANSPLANTATION

Maewal, I.[1], Kurtzweil, A.J.[1], Shapiro, J.F.[2], Westmoreland, M.D.[1], Bassett RL Jr., Jr.,[3], Giralt, S.A.[4] [1]MD Anderson Cancer Center, Houston, TX; [2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [3]MD Anderson Cancer Center, Houston, TX; [4]MD Anderson Cancer Center, Houston, TX

At MD Anderson Cancer Center, the standard-of-care preparatory regimen in patients with multiple myeloma receiving an autologous stem cell transplant is melphalan 200 mg/m^2 given over two days with one day of rest prior to transplant. The primary objective of this study is to determine if differences exist in the severity of toxicities in patients with multiple myeloma who receive melphalan as a preparatory regimen in three distinct treatment schema. The secondary objective of this study is to ascertain the differences in time to engraftment in this population. Toxicities, defined as nausea, vomiting, diarrhea, renal and hepatic dysfunction, were graded using the NCI-CTCAE. Pain secondary to mucositis was recorded based on the use of patient-controlled analgesia. We performed a retrospective review in patients who received one of the following preparatory regimens: arm 1) melphalan 200 mg/m^2 over days -3 and -2, arm 2) melphalan 200 mg/m^2 over day -2, or arm 3) melphalan 200 mg/m^2 over days -2 and -1. This review included patients over the age of 18 in first remission or with primary refractory disease who received autologous transplantation within 12 months of diagnosis. Patients who received prior transplantation were excluded from this review. 164 patients were identified from the institutional database for data collection and 100 patients were selected at random for this interim analysis. The majority of patients identified were male, <65, ISS stage of I-II, and had an ECOG performance status of 0–1. With respect to the primary endpoint, no statistically significant differences were observed in the severity of toxicity when comparing the treatment schemas (nausea: p = 0.55; vomiting: p = 0.46; diarrhea: 0.52, Kruskal-Wallis test and PCA use secondary to mucositis: p = 0.82, Fisher's exact test). With regard to time to engraftment, the actual difference between the arms was approximately 1 day, yet the comparison between the three groups was statistically significant (p<0.001, log-rank test). We concluded that differences between the three treatment schemas in the severity of toxicities were neither statistically nor clinically significant; the differences in time to engraftment were not clinically significant. Based on the interim analysis, this review demonstrates the potential for melphalan to be administered in any one of three distinct treatment schemas without resulting in adverse effects on toxicity and time to engraftment.

Results

	Arm 1 (N=44)	Arm 2 (N=37)	Arm 3 (N=19)
Grade 3-4 Toxicity	n (%)	n (%)	n (%)
Nausea	2 (4.5%)	1 (2.7%)	0
Vomiting	2 (4.5%)	0	0
Diarrhea	0	2 (5.4%)	0
Serum creatinine	0	0	0
Total bilirubin	0	1 (2.7%)	0
Pain	5 (11.4%)	4 (10.8%)	1 (5.3%)
Time to engraftment (median)	10 days	11 days	10 days

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SUCESSFUL OUTCOME AFTER ACCIDENTAL HIGH DOSE CYTARABINE (HIDAC) INFUSION SEVEN DAYS POST UNRELATED DONOR (UD) CORD BLOOD (CB) STEM CELL TRANSPLATION (SCT)

Stelts, S., Nath, R. Methodist University Hospital/University of Tennessee Cancer Institute, Memphis, TN

Introduction: The complex regimens of allogenic SCT increase the risk of medication errors. We report an accidental HIDAC infusion post UD-CBSCT and the patient outcome.

Case Report: A 24 year old heavily pretreated female with history of relapsed philadelphia (Ph) positive acute lymphoblastic leukemia received a 4/6 matched UD-CBST. The patient received a preparatory regimen of fludarabine 30 mg/m2 on days -7 to -3, melphalan 70 mg/m2 on day -3 and -2, and antithymocyte immunoglobulin 10mg/kg on days -4 and -2. Graft versus host disease (gvhd) prophylaxis consisted of tacrolimus (level 5 -15 ng/ml) and mycophenolate

mofetil (MMF) starting day -1. On day +7, the patient received an accidental dose of HIDAC 3700 mg/m^2 (6000mg) over 3 hours instead of MMF. Patient developed worsening of her nausea and vomitting but was controlled with antiemetics. She engrafted her neutrophils with her absolute neutrophil count (ANC) >500/μl on day +33 and >1000/μl on day +35 post SCT. She engrafted her platelets with her untransfused platelet count > 20,000/μl on day +43 and >50,000/μl on day +54 post SCT. Patient did not develop any acute gvhd. On day +36 the patient was discharged from the hospital. Patient had CNS relapse on day +71 (positive CSF cytology and leptomeningeal enhancement on an MRI) but no systemic disease (bone marrow biopsy 99–100% donor chimerisim and normal cytogenetics). The patient's treatment included intrathechal liposomal cytarabine 50 mg on day +72 and +96, HIDAC 3000 mg/m2 every 12 hours for 10 doses from day +77 to +82 and dasatinib 140 mg orally daily from day +78 to +83. Tacrolimus was discontinued on day +77. The patient was neutropenic for 37 days (day +84 to +120) but achieved a remission in her CNS. At day +175 patient is alive, disease free, without gvhd off all immunosuppression with normal ANC with 100 percent donor chimerism.

Discussion: There is no literature on HIDAC infusion post allogeneic SCT. Published data suggests that the longer duration of cytarabine exposure is more cytotoxic to hematopoietic cells than the dose. Other chemotherapeutic agents including methotrexate and cyclophosphamide has been given posttransplantation for gvhd prophylaxis and graft enhancement. HIDAC infusion post CBSCT did not significantly delay neutrophil or platelet engraftment as compared to published literature but may have contributed to lack of gvhd in this patient inspite of withdrawl of all immunosuppression by day +77.

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CIDOFOVIR USE IN THE ERADICATION OF POLYOMAVIRUS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Kenealy, L.K.[1], O'Neal, N.K.[1], Williams, C.B.[1], Wilhauk, J.[2], Hoffman, T.[2], Aljitawi, O.S.[2], Abyhankar, S.[2], McGuirk, J.P.[2], Ganguly, S.[2] [1] University of Kansas Hospital, Kansas City, KS; [2] University of Kansas Hospital, Kansas City, KS

Hemorrhagic cystitis caused by polyomavirus virus (BKV) is a common complication following high dose chemotherapy and hematopoietic stem cell transplant. Low dose cidofovir has been shown to be useful in the eradication of BKV post transplantation without significant side effects. Controversy exists over the effective dose, duration, and administration technique for cidofovir. Recent data shows utilization of a dose range of 0.25–1mg/kg IV weekly. The purpose of this review is to establish an optimal dose, duration, and monitoring standards for cidofovir use in a future prospective trial. This information will be further utilized at our institution to implement an evidence- based standard of practice. A retrospective review was completed on 13 patients with symptomatic BKV who received cidofovir during a 15-month period. Cidofovir dose was given without probenecid and initiated at 0.5mg/kg intravenously weekly. If no significant reduction in viral copies was seen, the dose was escalated to 1mg/kg. Patients were monitored for a molecular response in both urine and plasma for BK viral load. Molecular response was defined as a decrease in viral load by one log reduction with a consistent decreasing trend. Patients received cidofovir for an average of 7.6 weeks. Urinary response was shown in 7/13 (54%) and plasma response in 6/9 (67%) patients. Plasma PCR data was not measured in 5 patients. Transplant-related mortality occurred in 5 patients with 80% (4/5) not responding in the urine to treatment. Acute renal failure, defined as an increase of 0.5mg/dL from baseline, occurred in 1/13 (7.6%). Based on this data, we plan to enroll patients into a randomized study using 0.5mg/kg or 1mg/kg weekly intravenous cidofovir to determine the most effective treatment regimen for symptomatic patients while minimizing toxicity. Patients will have BKV PCR analysis weekly on blood and urine to determine eradication and optimal length of therapy. Data will be examined to determine if therapy can be discontinued based on clinical response or molecular response. Due to the renal dysfunction associated with cidofovir, serum creatinine will also be monitored. Results from this trial will be valuable since no current standard of care for BK viremia exist.

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ADDITION OF URSODIOL IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT TO REDUCE THE RISK OF VENOUS OCCLUSIVE DISEASE AND GRAFT VERSES HOST DISEASE

Kenealy, L.K.[1], Brinkman, J.L.[1], McFarland, K.L.[1], Williams, C.B.[1], Hoffman, T.[2], Wilhauk, J.[2], Aljitawi, O.S.[2], Ganguly, S.[2], McGuirk, J.P.[2], Abhyankar, S.[2] [1] University of Kansas Hospital, Kansas City, KS; [2] University of Kansas Hospital, Kansas City, KS

Venous-occlusive disease (VOD) and graft-versus-host disease (GVHD) are devastating complications of allogeneic hematopoietic stem cell transplants (HSCT). Mortality has been estimated to be as high as 30% for VOD and 40% for GVHD, which remains the main cause of morbidity associated with HSCT. The use of prophylactic ursodiol is believed to provide protection against complications. However, clinical evidence for the use of this medication is limited and the duration of therapy has not been established in non-myeloablative pre-transplant regimens. The primary objective of this retrospective review is to determine the incidence and severity of VOD and GVHD in allogeneic HSCT patients not receiving prophylactic ursodiol. Thirty-four patients that underwent allogeneic HSCT in 2007 who did not receive ursodiol prophylaxis were evaluated. Acute GVHD was staged as level 0–4 based on quantification of skin rash, serum bilirubin, and gastrointestinal tract involvement. Chronic GVHD will be graded as level I-IV based on the degree of skin and organ involvement and clinical performance status. VOD will be graded based on the Baltimore criteria which include jaundice (bilirubin ≥ 2.0 mg/dL) and two of the following: hepatomegaly, ascites or ≥ 5% weight gain. Chronic GVHD and VOD data is yet to be determined. Stage of acute GVHD in patients that were evaluated is shown below in table 1.

Acute GVHD incidence in 34 patients

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
26% (n=9)	29% (n=10)	32% (n=11)	8.8% (n=3)	3% (n=1)

Acute GVHD was seen more often in non-myeloablative (average grade 1.6, n = 15) versus myeloablative protocols (average grade 1.2, n = 19). The second phase of this trial will evaluate the incidence of VOD and GVHD in patients who receive prophylactic ursodiol. This data will be compared to the patient population that did not receive prophylaxis to determine the outcome. This data will be helpful in determining the effectiveness of prophylactic ursodiol in non-myeloablative HSCT.